REMARKS

Election/Restriction

The Examiner withdrew claims 4 and 7-9 as allegedly being directed to an invention that is independent or distinct from the invention as originally claimed. Applicants respectfully request reconsideration of the restriction requirement.

Applicants respectfully disagree with the Examiner's assertions that original claim 4 was drawn to a product and point out that original claim 4 was directed to "The use of a mutant strain ... for obtaining a vaccine". Moreover, the Examiner examined original claim 4 because the Office Action of 17 April 2009 rejected claim 4 under both a utility rejection and an indefiniteness rejection.

Applicants assert that the Office Action fails to explain why the inventions are independent and distinct. Instead, the Office Action simply asserts that the newly amended claims are drawn to a method and product, and the originally filed claims are drawn to a product. Applicants respectfully remind the Office that there must be an explanation as to why the inventions are separate and distinct, and it must be demonstrated that there would be a serious burden on the Examiner if a restriction were not made. Applicants assert that the Office Action fails to demonstrate either of the required elements. In particular, the Office Action fails to explain why the product claim of claim 1 is independent and distinct from the product claim of claim 9. Claim 9 is dependent product claim directed towards a composition that comprises the product of claim 1. Applicants respectfully request at least rejoinder of claim 9 to claims 1 and 6.

In addition, Applicants respectfully request that the Examiner indicate that claims 4, 7 and 8 are eligible for rejoinder. Applicants assert that claim 4 is a process claim related to claims 1 and 6 as a product and method of use. Claims 7 and 8 further depend on claim 4 and are methods of use claims that are related to the product claims. Upon indication that the product claim is allowable, Applicants assert that at least claim 4, and possibly claims 7 and 8, be rejoined and deemed allowable provided that the claims contains all the elements of the allowed product claims. Applicants respectfully request notification of possible rejoinder of claims 4, 7 and 8 to claims 1 and 6.

Priority

Applicants will provide a certified copy of the priority document in due course.

Withdrawn Objections/Rejections

Applicants thank the Examiner for withdrawing the previously presented objection and rejections as indicated in the January 20th Office Action.

The Specification Fully Supports the Claimed Invention

The rejection of claim 6 under 35 U.S.C. § 112, first paragraph, because the claims allegedly contain subject matter that was not described in the specification in a way as to enable one skilled in the art to make and/or use the invention. Applicants respectfully disagree. Applicants have amended the claims to better capture the envisioned commercial embodiments and assert that the claim amendments render moot the enablement rejection.

In addition, Applicants provide the following comments regarding the guidance provided in the specification and the state of the art at the time of filing. Three major genotypes are known for *T. gondii* strains: types I, II and III. Type I strains are characterized by an important virulence in mice. Cysts, however, are rarely if ever developed from this strain type. Type II strains, on the other hand, are avirulent. An infection a type II strain can lead to death during the acute phase only at a high dosage or if mice have an increased sensibility to acute infection. Type II strains are responsible for the chronic phase of toxoplasmosis. Type III strains comprise both avirulent and intermediately virulent strains.

In the Examples in the present application, the RH strain that is used as the vaccine strain is a type I strain, whereas strains 76K and PRU, used are used as the challenge strains, are type II. The application expressly demonstrates that the vaccine obtained from a type I strain provides cross protection against infections with type II strains. The application provides experimental results on mice (Example 4) and ewes (Example 5). Example 4 discloses vaccination of mice infected with type II strain 76K and Example 5 discloses vaccination of ewes infected with type II strain PRU.

With respect to Example 4, when studying infection with *T. gondii* in mice, Applicants assert that one skilled in the art would recognize that the criterion to be measured is brain cysts number. Given that type I strains rarely, if ever, result in cyst formation, infection with a type II *T. gondii* strain is ideal for use in challenge experiments. Strain 76K is for example usually used in mice. *See* for instance Debard *et al.* (Infect. Immun. 1996 Jun, 64(6):2158-66; *copy here enclosed*), wherein strain 76K was used as a challenge strain to study immunization with a specific product association in mice. Debard *et al.*

measured the amount of brain cysts in order to evaluate the protection of mice against infection with *T. gondii*, identical to Example 4, and concluded that this association allowed protection against chronic toxoplasmosis. Accordingly, Example 4 clearly demonstrates effective vaccination of mice with a vaccine obtained from a mutant type I strain against infection by a type II strain.

As regards Example 5, when studying infection with *T. gondii* in ewes, one skilled in the art would know that the criteria to be measured are abortions and lamb deaths rate. *See* for instance Dubey (Vet. parasit. 2009; 163: 1-14; *copy here enclosed*), in particular paragraph 3.1 (page 9) and Table 5, wherein ewes are inoculated orally with oocysts and infection with toxoplasmosis is evaluated by measuring fever, abortion and lamb death, identical to Example 5 in the Application. Accordingly, Example 5 would confirm to one of skill in the art that effective vaccination of ewes with a vaccine obtained from a mutant type I strain against infection by a type II strain. The results in Example 5 are consistent with the mouse experiment results of Example 4.

Also, in Example 5, febrile abortions and infectious abortions are distinguished. Febrile abortions occur earlier in time than infectious abortions and are due to the increase of the temperature of ewes caused by the infection.[1] This fever episode directly depends on if the animal is infected, *i.e.,* if and when the vaccination was carried out and if it was effective. As explained in the Application (p. 31, l. 37 to p. 32, l. 18), vaccinated ewes had a shorter and less intense fever episode after infection compared with non-immunized ewes. All abortions, whether febrile or infectious, can reasonably be assumed to be due to infection with toxoplasmosis. So, the fact that fewer abortions (febrile + infectious) were seen in vaccinated ewes in Example 5 is proof that vaccination with the mic1-3KO strain is an efficient form of protection.

As a consequence, the experimental protocols followed in Examples 4 and 5 in the instant application are protocols generally recognized in the art in order to study infection with *T. gondii* respectively in mice and ewes. Based on the state of the art at the time of filing and based upon the guidance provided in the specification, Applicants assert that a person having ordinary skill in the art

[1] Applicants also note that Dubey discloses various experiments wherein no distinction is made between febrile abortions and infectious abortions. Any abortion was considered when evaluating an infection with toxoplasmosis.

would have no reason to doubt that the vaccine of claim 6 is efficient, in particular against any type II strain.

Furthermore, type II strains are predominant in sheep and human toxoplasmosis, as reported in Owen *et al.* (J. Parasitol. 1999 Apr.; 85(2): 382-4; *abstract here enclosed*) and Ajzenberg *et al.* (J. Infect. Dis. 2002; 186: 684-9; *copy here enclosed*), respectively. The person having ordinary skill in the art would have no reason to doubt that the vaccine of the invention is an efficient vaccine, in particular for humans and sheep.

In other words, the instant Application expressly discloses that a vaccine comprising type I mutant strain RH mic1-3KO is effective on mice infected with type II strain 76K (Example 4) and on ewes infected with type II strain PRU (Example 5). From these results and from state of the art at the time of filing, one skilled in the art would reasonably conclude that (1) the claimed vaccine would be effective against infection with any type of strain, in particular in sheep and humans, as type II strains, (2) the claimed vaccine would be effective against infection with any type I strain as the vaccine strain is itself a type I strain. This conclusion is corroborated Penarete-Vargas *et al.* (Infect. Immun., 2010 Feb., 78 (2): 651-60; *copy here enclosed*), which showed a 100% survival rate in mice immunized with mic1-3KO and subsequently challenged with *T. gondii* RH strain (page 656 and Fig. 3B). Penarete-Vargas *et al.* also shows that the mutant strain mic1-3KO as used in the instant Application confers a protection with respect to an infection against *Neospora*. Thus, if this mutant strain confers protection against Neospora, one of skill would expect that the mutant strain would confer protections against any strain of *T. gondii*, since the differences between *Neospora* and the *T. gondii* RH strain would be greater than the differences between the RH strain of *T. gondii* and any other strain of *T. gondii*.

Applicants assert that it would not require undue experimentation for one of skill the art to implement the invention of claim 6 in view of the instant specification and the general knowledge in the field of the invention. Applicants respectfully request reconsideration and withdrawal of the enablement rejection.

The Claims are Not Obvious

Claims 1 and 6 were rejected under 35 U.S.C. § 103 as allegedly being unpatentable over Meissner *et al.* (J Cell Sci. 115:563-574 (2002)). Applicants respectfully disagree. Applicants have amended the claims to better capture the envisioned commercial embodiments and assert that the

claim amendments render moot the obviousness rejection. Applicants respectfully request reconsideration and withdrawal of the obviousness rejection.

Meissner relates to the study of microneme proteins of *Toxoplasma gondii* and more particularly the characterization of proteins TgMIC6, TgMIC7, TgMIC8 and TgMIC9. The cited reference mainly concerns the interactions between various microneme proteins of *Toxoplasma gondii* during their transport to the organelles to which they are intended. In particular, the authors showed the role of TgMIC6 as an escorter of adhesins TgMIC1 and TgMIC4, and the role of TgMIC8 as an escorter of adhesin TgMIC3. In Meissner, strain mic1ko is used within the framework of the determination of the topology of TgMIC6 during its transport and its storage in the micronemes.

Mutant strain mic1ko is also used in the invention to prepare the mutant strain mic1-3KO. However, as the Examiner concedes, Meissner does not describe or suggest a mutant strain of *T. gondii* in which gene MIC3 would be inactivated, and even less one mutant strain of *T. gondii in* which genes MIC1 and MIC3 would be inactivated. Accordingly, Applicants assert that the Meisser does not render obvious the currently claimed invention because Meissner does not teach each and every element of the claimed invention.

In addition, concerning the obviousness to carry out a double mutation, as it was noted by Ismael *et al.* (JID 2006:194, 1176-1183; *copy here enclosed*), inactivation of gene MIC1 is equivalent to carrying out a triple inactivation because of the close relations existing between MIC1, MIC4 and MIC6 (page 1177, left column, last line). Moreover, it is known that the multiplication of the mutations increases the risk of the strain not being viable. Therefore, the person having ordinary skill in the art would not have been motivated to inactivate another protein in addition to MIC1.

Meissner also describes a mutant strain mic1ko and mentions the roles of MIC1 and MIC3 in the interactions between microneme proteins within *T. gondii*, but does not consider at all the interest of these proteins in the framework of the preparation of a vaccine, or even the effects of a double mutation mic1-3KO, which in itself is neither disclosed nor suggested. In particular, Meissner discloses that TgMIC1, TgMIC3 and TgMIC4, as adhesion proteins, are able to bind to a host cell but Meissner does not describe or suggest that the inactivation of one or the other of these proteins, or even of several of them, would result in obtaining strains that have lost their virulence *in vivo*, yet preserving immunogenic properties similar to those of the virulent wild strains, in order to induce an immunizing protection

against those. Thus, Meissner would not provide any reasonable expectation of success in carrying out the currently claimed invention.

Moreover, Applicants assert that the Office Action fails to a reasonable explanation as to why a person having ordinary skill in the art would combine the mutations of MIC1 and MIC3 rather than those of MIC1 and MIC4 or MIC3 and MIC4, for example. In fact, as stated above, Applicants assert that Meissner would have motivated the person of ordinary skill in the art *against* carrying out the claimed invention. Indeed, Applicants assert that the person having ordinary skill in the art would not have been motivated by Meissner to choose as a second MIC3 gene Meissner provides no indication or suggestion that mutation of this gene rather than another would have had a clinically relevant effect.

Finally, Applicants assert that, based on the state of the art at the time of filing, a person having ordinary skill in the art would have considered that the immunogenic potential of the mutant strain was likely to be seriously affected by the loss of two major antigens, and would thus not have considered, in an obvious way, to inactivate MIC1 and MIC3 in order to obtain a vaccine. Indeed, the supplied references disclose proteins MIC1 and MIC3 as being major antigens. For example, Bourguin *et al.*, Infection and Immunity, 4867-4874, 1998 (*cited in the International Preliminary Report on Patentability and in the IDS filed on 7/12/2006*) clearly mentions MIC1 among the major antigens which can induce a protective immunizing response with respect to *T. gondii* (page 4872, left-hand column, last paragraph).

Applicants respectfully request reconsideration and withdrawal of the obviousness rejection.

CONCLUSION

Applicants have amended the claims to better capture the envisioned commercial embodiments and assert that the claim amendments render moot the outstanding rejections.

Should the Examiner believe that further discussion of any remaining issues would advance the prosecution, he or she is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,

Date 21 June 2010 By /Todd B. Buck/

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